American Journal of Hematology / Volume 87, Issue 10

Critical Review | Free Access

Bleeding and mortality outcomes in ITP clinical trials: A review of thrombopoietin mimetics data†

Ivy Altomare ✉, Jeffrey Wasser, Vinod Pullarkat

First published: 22 June 2012
https://doi.org/10.1002/ajh.23275
Citations: 9

† Conflict of interest: Advisory Board and Speaker Bureau for Amgen.

Abstract

Patients with ITP may have severe thrombocytopenia, putting them at risk for serious bleeding. ITP trials of new treatments must allow use of standard-of-care therapies to prevent serious bleeding. Thrombopoietin mimetic trials used platelet counts and rescue/concomitant medication use as endpoints. These trials were of insufficient size and duration to measure mortality or serious bleeding, which are infrequent with appropriate treatment. A recent Cochrane review criticized the thrombopoietin mimetic registrational trials for inadequately assessing bleeding and survival. We discuss how these endpoints are difficult to measure in clinical trials designed to improve platelet counts and minimize bleeding, in accordance with ethical trial design. Am. J. Hematol. 2012. © 2012 Wiley Periodicals, Inc.

Introduction

While ITP is generally a benign disease, the risk of mortality in affected patients is roughly twice that of the general population, particularly in patients who are older or who have more advanced disease with a history of bleeding [1-6]. Causes of death in ITP include seve bleeding, such as gastrointestinal and intracranial hemorrhage, post-splenectomy complications, and infections secondary to long-term immunosuppression from ther Infection and bleeding are the most frequently reported causes of death in ITP, with one study reporting death due to infection as being more common than death due to bleeding [2, 3]. Hospitalizations in adults with ITP are on average more costly, longer, and associated with higher mortality than hospitalizations within the US population as a whole [6].

- **Persistent or Chronic ITP** — Chronic ITP is treated either when the platelet count falls below 30,000, or when there is bleeding; steroids (such as prednisone) is often the first choice of treatment. If steroids do not keep the platelet count above 50,000, or the dose of steroids needs to remain high, then doctors most often order intravenous gamma globulin.

If these treatments are not effective and the platelet count remains dangerously low or there is bleeding, other options include removal of the spleen (splenectomy), treatment with rituximab (Rituxan), Romiplostim (Nplate) or Eltrombopag (Promacta, Revolade). If these initial treatments aren't effective, tranfusions, fostamatinib (Tavalisse), danazol (Danocrine) or immune-suppressing medications (such as azathioprine (Imuran), cyclophosphamide (Cytoxan, Neosar), or vincristine (Oncovin and others)) may be recommended. Combinations of these treatments may be effective when individual treatments are not.

Patients who have undergone spleen removal need to be aware that they are at significant increased risk for the development of certain types of infections and should receive a number of vaccinations.

All medications, foods and beverages will be reviewed to be certain that they do not contain an ingredient that may have triggered the ITP. For example, in certain people, ingesting quinine (as in tonic water) can cause a low platelet count.

During treatment for ITP, you or your child will be advised to avoid sports and other physical activities that have a high risk of injury, especially head injury.

When To Call A Professional

Call your doctor if you have had episodes of abnormal bleeding, including easy bruising, prolonged oozing from small cuts , abnormal menstrual bleeding, or prolonged bleeding after minor surgery or dental procedures.

If you are a parent, call your pediatrician or family doctor if your child develops signs of abnormal bleeding, such as easy bruising, a red or purple rash, lots of tiny purple spots (petechiae),frequent or heavy nosebleeds, bleeding gums or blood blisters inside the mouth or lips.

Prognosis

For children, the outlook for acute ITP is generally very good. About 75% of patients recover completely within three months, and about 80% recover within six months. Less than 1% of children with ITP develop bleeding within the skull. Only a small percentage of children go on to develop chronic ITP, and most of these children do not have serious bleeding.

Symptoms of chronic ITP usually come and go in adults. When medication is necessary, about 50% of patients who are treated with prednisone have normal platelet counts within four to six weeks. However, when the prednisone is reduced, the platelet count drops again in many people. If this happens, doctors may recommend that the person's spleen be removed. Within one week of having the spleen removed, about 70% of adult patients with chronic ITP have normal platelet counts. The risk of removing the spleen is an increased risk of infections.

Additional Info

National Heart, Lung and Blood Institute (NHLBI)
http://www.nhlbi.nih.gov/

National Institute of Allergy and Infectious Diseases (NIAID)
http://www.niaid.nih.gov/

American Academy of Family Physicians (AAFP)
http://www.familydoctor.org/

Symptoms

ITP does not usually cause symptoms as long as your platelet count remains above 50,000, which is typically the minimum needed to prevent abnormal bleeding. At lower platelet levels, ITP can cause different symptoms, depending on the type of ITP.

Sometimes, the only symptom is the appearance of tiny purplish spots that show up on the lower legs. They are called petechiae. These are pinpoint size accumulations of blood under the skin caused by leaky small blood vessels.

At very low platelet levels, ITP can cause different symptoms, depending on the type of ITP.

- **Acute ITP** — Symptoms usually begin abruptly. In children, the trigger can be a viral infection, with ITP symptoms appearing one to three weeks after the infection resolves. In adults, the trigger for acute ITP may not be obvious. The first sign of the illness may be a red or purple skin rash on the legs or abnormal bruising after only minor trauma. There also may be small areas of bleeding or "blood blisters" on the surface of the lips or gums, and frequent or severe nosebleeds.
- **Persistent or Chronic ITP** — A typical patient with persistent or chronic ITP is an adult woman who has had intermittent episodes of unexplained bruises, cuts that tend to heal slowly and ooze blood, prolonged bleeding after tooth extractions, and unusually long or heavy menstrual periods

Diagnosis

It's important that you tell your doctor about all prescription and nonprescription drugs, natural or herbal remedies that you or your child is taking. Your doctor will examine you or your child with special attention to any rashes, areas of bruising, oozing cuts or other signs of abnormal bleeding. Your doctor will order one or more of the following tests:

- A blood platelet count — Doctors always order this test first. ITP is one of the causes of a low platelet count (thrombocytopenia).
- Other blood tests — Several different blood tests may be done, including a test for HIV and hepatitis C.
- A blood smear — In this test, a drop of blood is smeared on a glass slide so that the size, shape and general appearance of the platelets and other blood cells can be checked under a microscope.

Depending on the results of these tests, a bone marrow biopsy may be recommended, especially if the patient is a child who has not had an infection recently or an adult who has had abnormal bleeding on and off for a long time. In a bone marrow biopsy, a small piece of bone marrow is removed and examined in a laboratory.

The purpose of this test is to determine whether cells called megakaryocytes are present. Megakaryocytes are the bone marrow cells that turn into platelets.

In ITP, there should be a plenty of megakaryocytes. This indicates that the bone marrow is working normally to produce new platelets.

If few megakaryocytes are seen, other diagnoses need to be entertained, such as leukemia or other bone marrow disorders.

Expected Duration

Newly diagnosed (acute ITP) lasts for three months or less; in children with acute ITP, about 75% recover on their own within two to three months. Persistent and chronic ITP tends to come and go over many years.

Prevention

There is no way to prevent ITP. If a medication has caused the condition, stopping the medication may cure the condition; avoiding this medication in the future may prevent recurrence.

Treatment

Treatment varies, depending on whether ITP is acute, persistent or chronic:

- **Acute ITP** — Because people with acute ITP often recover without treatment, doctors may not prescribe medications unless the platelet

Immune Thrombocytopenic Purpura (ITP)

What Is It?

Published: December, 2018

Immune thrombocytopenic purpura (ITP), also known by the shorter name Immune Thrombocytopenia (same abbreviation ITP), can be understood by looking at the three terms that make up its name:

- **Immune** indicates that the illness is caused by the immune system, which makes cells and antibodies that attack the person's own platelets — the parts of the blood that help the blood to clot.
- **Thrombocytopenic** means that the illness is related to low levels of thrombocytes, another name for platelets. Platelets are produced in the bone marrow (the central lining of the bones). The body needs adequate numbers of functioning platelets to allow blood to clot and to limit bleeding if you are cut or experience other types of trauma.
- **Purpura** means that the illness produces a red or purple rash that is caused by bleeding under the skin. This is only one manifestation of the disease

In short, ITP is an illness in which unusually low levels of platelets lead to purpura and other forms of abnormal bleeding.

In people with ITP, the immune system produces abnormal proteins called antiplatelet antibodies. These misdirected proteins attach themselves to the surface of blood platelets as if the platelets were "foreign" or invading bacteria or viruses. As the affected platelets circulate in the bloodstream, they are recognized as abnormal by the spleen and removed from the blood.

As more and more platelets are removed by the spleen, the level of platelets in the blood drops past the lower limit of normal (about 130,000 per cubic millimeter of blood) and the patient is diagnosed with thrombocytopenia (low platelet count).

When platelet levels fall into the 30,000 to 50,000 range, a person may begin to have abnormal bleeding after a minor skin injury, such as a small cut, bruise, medical injection, blood test or tooth extraction.

If platelet levels fall below 10,000, the person has an increased risk of bleeding even when no injury has occurred. This type of bleeding is especially dangerous if it happens inside the skull and brain, where it is known as an intracranial hemorrhage. Bleeding may also occur in the kidneys and bladder causing bloody urine. Excessive bleeding can also occur during normal menstrual cycles.

There are currently three classifications of ITP:

- **Newly diagnosed (also referred to as acute) ITP** — This form of ITP lasts for less than three months and typically affects children, most commonly those between the ages of 2 and 6. It usually appears shortly after a viral infection. Most children with acute ITP recover without treatment, and their platelet counts eventually rise to normal levels. However, 7% to 28% of people with newly diagnosed ITP go on to develop either persistent or chronic ITP.
- **Persistent ITP:** Here, the disease has been present for 3 to 12 months, and has not undergone spontaneous correction or remission on its own. It still is persistent in the face of several trials of treatment.
- **Chronic ITP** — This form of ITP lasts for more than 12 months, usually strikes adults between the ages of 20 and 40, and requires medical treatment to restore normal platelet levels. Chronic ITP is three times more common in women than men. Typically, a person has weeks or months of mild to moderate abnormal bleeding off and on before seeing a doctor.

In most cases, the cause of ITP is unknown. In a few cases, ITP can be a reaction to a specific drug or food ingredient, such as quinine in tonic water. In the United States, ITP is a relatively rare illness that affects about four out of every 100,000 people each year